Potential Role of Environmental Factors in the Etiology and Pathogenesis of Atopy: A Working Model

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Sensitization to inhalant allergens commonly commences *in utero*, and most children are born with weak T helper-2 (Th2)-polarized T-cell immunity to these agents. During early life, these responses are normally deviated toward the Th1 cytokine profile. However, in atopics this immune deviation process fails, leading instead to consolidation of allergen-specific Th2 immunity and its eventual active expression in the airways. Both the induction and expression of Th2 immunity can be modulated by environmental agents that affect the cytokine milieu in the airway mucosa and/or the draining lymph nodes. Because of the known effects of the mold cell wall component (1→3)-β-D-glucan on monocyte cytokine secretion, exposure to molds during childhood may be a significant etiologic factor in allergic respiratory disease in general. *Key words*: atopy, (1→3)-β-D-glucan, LPS, molds, T-helper cells. — *Environ Health Perspect* 107(suppl 3):485–487 (1999).
http://ehpnet1.niehs.nih.gov/docs/1999/suppl-3/485-487holt/abstract.html

It is generally accepted that the development of the immune system in children is sensitive to environmental agents. In particular, growing evidence indicates that the development of immunity to inhaled antigens can be influenced by coexposure to airborne irritants, which can influence the functions of bone marrow-derived cells. There is also indirect evidence from human epidemiologic studies (*1*) that exposure of school children to molds can exacerbate atopic symptoms.

This article describes a working model for the interaction between the environment and immune function in children and illustrates how exposure to molds could be a significant modifying factor.

Immunologic Features of the Natural History of Allergic Respiratory Disease

Allergen-Specific Immunity in Adults

It is now generally accepted that active T-cell immunity against common inhalant allergens is universal among adults, and allergen responder phenotype is determined by the nature of the cytokines produced by allergen-specific T helper (Th) memory cells at each exposure (*2,3*). Thus, if the dominant Th cells in respective memory populations produce the Th2 pattern of cytokines (especially interleukin [IL]-4 and IL-5), exposure will potentially trigger IgE production and eosinophilia, and hence allergic symptoms, as in atopics. In contrast, if the dominant Th-cell populations produce only low levels of Th1 cytokines (IL-2 and IFNγ), allergen exposure will

result in only moderate IgG and IgA antibody production and no symptoms. Additionally, the expression of Th1 immunity actively inhibits Th2 responses via antagonistic effects of IFNγ upon Th2 cell growth.

Initial Priming of Allergen-Specific Th Memory Cells

Recent evidence from a number of laboratories [reviewed in Holt and Macaubas (*4*)] indicates that the process is normally initiated *in utero* via transplacental leakage of extremely low levels of allergens to which the mother is exposed during pregnancy. This low-level stimulation occurs at a time during which placentally derived factors including cytokines, prostaglandins, and hormones are actively inhibiting all forms of Th1 immunity at the fetomaternal interface to protect the placenta against the toxic effects of IFNγ (*5, 6*). These initial fetal responses are thus polarized toward the Th2 cytokine profile (*7,8*).

Postnatal Modulation of Fetally Primed Allergen-Specific Th Cell Responses

After birth, the newborn immune system encounters high levels of inhalant allergens from the environment and these repeated cycles of Th-cell stimulation shape the nature of developing Th memory populations.

In normal (nonatopic) children, these early Th2 responses are progressively converted to Th1 via a process known as immune deviation (*4,6*), and Th memory patterns similar to those of adults are seen

by approximately 5 years of age (*9*). However, for reasons not yet fully understood, this immune deviation process frequently fails in children with atopic family history, leading instead to consolidation of allergen-specific Th2 immunity, and hence heightened risk for allergy (*9*). This may be due in part to a transient maturational defect in Th1 function in atopics (*4,6*).

Induction Versus Expression of Allergen-Specific Th2 Immunity

Inhalant allergen-specific Th2 immunity per se does not automatically lead to allergic respiratory disease, as demonstrated in a variety of epidemiologic studies. Up to 40% of preteen school children are Th2 responsive to one or more inhalants, but only one-quarter of these go on to develop bronchial hyperresponsiveness (BHR) and persistent wheeze; the latter proportion increases only to approximately one-third by adulthood. However, more than 90% of both children and adults who express BHR are atopic, indicating that atopy is necessary but not sufficient for development of airway symptoms.

What Is the Missing Factor?

Immunopathologic studies from many laboratories suggest that the ultimate development of chronic BHR is the result of repeated cycles of inflammatory damage in the tissue (*10*). The initial trigger for this process among atopics is allergen-specific Th2 responses, but clearly other additive/synergistic factors are required for disease expression.

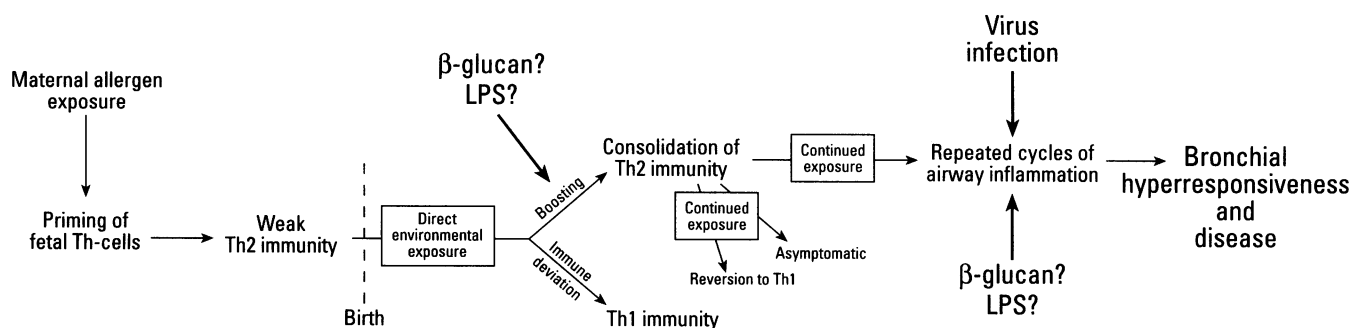An increasing body of evidence suggests that environmental factors capable of

Figure 1. Immunologic processes underlying the induction and expression of allergic respiratory disease—the potential role of β-glucan and other microbial associated factors. Abbreviations: LPS, lipopolysaccharide; Th, T helper.

modifying immunoinflammatory processes at the level of the airway mucosa or of triggering local inflammation directly may play a key role in this context.

Working Model

The scheme in Figure 1 provides a working hypothesis for this overall process. Weakly primed fetal Th2 responses are normally immune-deviated postnatally to protective Th1 immunity, but a subset of children (in our experience, up to 35%) are at risk because instead they consolidate Th2 immunity against one or more inhalant allergens. Of this at-risk group, only 1/4–1/3 ultimately develop chronic wheeze, and it is hypothesized that the latter group receives additive/synergistic inflammatory signals from nonallergen sources in the environment, which further stimulate local airway tissue damage to levels above the threshold required to trigger disease expression (BHR).

The best documented of these environmental factors is respiratory virus infection, which has been identified as a major trigger for asthma exacerbation in subjects with pre-existing atopy (11), particularly in school children. Air pollution may also play a role, although the effects are probably relatively minor except in extreme circumstances (12). Furthermore, microbial cell wall constituents such as endotoxin (13,14) and molds (14) interfere with cells engaged in the inflammatory–immune process. Molds are well-known antigens and may also cause nonspecific inflammatory response. In their cell walls they contain (1→3)-β-D-glucan with well-known inflammatory and immunogenic properties (15,16).

(1→3)-β-D-glucan causes cell infiltration in lung tissue and a reduction of antibody formation to an inhaled antigen (17). In a mouse model, the normal

downregulation of the allergen-specific IgE response was abrogated by glucan exposure (18). Other studies have demonstrated that exposure of inflammatory cells to (1→3)-β-D-glucan can trigger secretion of mediator molecules known to influence immune responses (19).

Depending on the dose and timing of the exposure, environmental agents could exert effects on at least two levels, as illustrated in Figure 1.

Th1/Th2 Regulation during Th-cell Memory Development. The postnatal modulation of fetally primed Th-cell responses to allergens is regulated principally by antigen-presenting cells (APCs) in the airway mucosa such as macrophages and dendritic cells. These express surface receptors for β-glucan. The triggering of these receptors is likely to influence a variety of their functions associated with allergen uptake and processing (particularly cytokine secretion), all of which can modulate ensuing Th-cell responses. The influx and efflux of local APCs is also regulated by the intensity and frequency of exposure to local microbial stimuli (20).

Expression of Allergen-Specific Th2 Responses in the Airway Mucosa. The defining feature of atopic asthma is the presence of large numbers of activated Th cells in the airway mucosa. The activity of these cells is in turn regulated by inductive signals from local APCs and by their secreted (cytokine) products. As indicated above, co-exposure to β-glucan has the potential to modulate the functions of these APCs.

Recent studies from several laboratories indicate that secreted products from alveolar macrophages play a key role in regulating the tonus of immunoinflammatory responses in the airways (21,22). Macrophages have specific receptors for (1→3)-β-D-glucan, and alterations in the

normal function of macrophages have been found after exposure to (1→3)-β-D-glucan (23).

In summary, the nature of immune responses to inhaled allergens during the early postnatal period is now recognized as a key factor in determining allergen responder phenotype in later life. Airborne environmental factors can potentially influence these responses. Exposure to mold components has not previously been studied in detail in this context, but further research in this area appears justified.

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